

## **REMARKS**

### **INTERVIEW WITH THE EXAMINER**

Applicant and Applicant's counsel greatly appreciated and thank Examiner Foreman and Supervisor Shukla for holding a telephonic interview with Applicant and his Counsel on August 25, 2006 regarding the Office Action and proposed amendments and arguments. In that interview it was suggested and agreed that if Applicant amends the claims to more clearly describe the detection step as being done without the presence of any solid support in connection with the construct-compound complexes that are being detected, the references and rejections should fall. The present Amendments and Remarks are submitted in view of the interview in order to place the claims in condition for allowance.

### **THE AMENDMENTS AND REASONS FOR AMENDMENTS**

Applicant amends claims 1 and 23. The amended claims add no new subject matter and are fully supported by the application, including the specification, examples, figures, and claims as originally filed.

For example support for the detection being done without the presence of any solid support in connection with the construct-compound complexes that are being detected can be found, for example, on page 7, lines 7-9:

The present invention is also generally more versatile because detection occurs in the solution phase and is not restricted to solid phase detection.

Further support for the amendments can be found, for example on page 2, lines 17-22:

The present invention recognizes that compound detection methods can be made more sensitive and thereby more effective by separation from the solution any excess or unbound binding construct that is not bound to the compound of interest, thus increasing the proportion of true "positive" signal to false "positive" signal. The present invention further provides a versatile detection system that does not require solid-phase capture or detection of the compound of interest.

**THE REFERENCES CITED BY THE EXAMINER FAIL TO ANTICIPATE THE CLAIMED INVENTION  
UNDER 35 U.S.C. § 102**

The Examiner rejects claims 1-3, 6-10, 15-17, 22-25, 28-32, 37-39 and 44 under 35 U.S.C. § 102(e) as allegedly being anticipated by Ullman et al. (US Pat. No. 6,797,481). The Examiner alleges that Ullman et al. teach a method for detecting a compound of interest in a sample which anticipates the rejected claims.

The applicant respectfully disagrees with the Examiner. Ullman et al. describe a multi-step process involving the binding of one or more analytes (drugs) in solution with antibodies (anti-drug antibodies in Example 1). Ullman et al.'s main purpose for the development of this assay system was to identify quickly and without quantification, the presence of drugs in biological fluids. An immediate difference with reference to the claimed invention is that the claimed invention does not use free antibodies in solution, but instead uses single binding domains with a nucleic acid template, hence a conjugated antibody binding domain or binding construct. In addition, the purpose of the present invention was to develop a sensitive and specific assay platform to identify and quantify specific analytes at low concentration in biological fluids. Multiplexing in the present invention would reveal the presence of individual molecules. Multiplexing in the Ullman et al. format will not distinguish among the individual molecules present in a sample.

In the Ullman et al. assay and the claimed invention, as in any solution-based immunological reaction, after the addition of the antibodies (binding construct of the claimed invention) to a sample, there are bound (to the analyte of interest) and unbound species in present in the solution.

In the Ullman et al. assay there is added to this solution of bound and unbound antibodies, a solid phase (sensitizer beads) that is "... a conjugate comprising (i) a first label (ii) a small molecule and (iii) a drug analogue ..." Claim 1(b), Col. 37, lines 46-48 (In the case of Example 1, drug-digoxin (small molecule)-bis-biotin-linked beads). This solid phase now binds to any unbound antibody. After placement in an instrument and suitable incubation time, a second solid phase is added to this mixture. This solid phase is "... a conjugate comprising (i) a second label and (ii) an antibody for said small molecule..." Claim 1(c), Col. 37, lines 50-52 (In the case of Example 1 anti-digoxin labeled chemiluminescer beads).

In the Ullman et al. assay, if drug is present it will bind to some or all of the antibodies. The remaining antibodies will bind to the sensitizer beads. Anti-Drug antibodies, bound to the sensitizer beads, presumably, sterically inhibit the binding of the anti-digoxin chemiluminescer beads. More drug means more signal. The Ullman et al. assay uses the presence of the unbound antibody as the means to indirectly measure the presence of the drug because more unbound antibodies will reduce or eliminate the signal. It should be noted that the Ullman et al. assay requires two solid phases for measurement. In contrast to the Ullman et al. assay, the claimed invention detects bound antibody and measures it directly bound to the analyte of interest in the solution phase, that is, in the claimed invention detection is done without the presence of any solid support in connection with the construct-compound complexes that are being detected.

The Ullman assay requires multiple steps and the addition of two solid phase reagents that are crucial for the assay and will give only a 'yes' or 'no' answer. The claimed invention is elegantly more simple and direct. In the present invention unbound binding construct (not antibody) is removed and solution phase bound antibody is detected and the assay is easily quantified, for example by using Real Time PCR amplification. In contrast to Ullman et al. the claimed invention requires no solid phase capture of analyte and no wash step in the detection step.

Thus, in view of the foregoing, Ullman et al. does not anticipate the claims. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

**APPLICANT'S CLAIMED INVENTION IS NOT OBVIOUS UNDER 35 U.S.C. § 103(A) IN VIEW OF THE REFERENCES CITED BY THE EXAMINER**

The Examiner rejected claims 1-11, 15-17, 19, 21-33, 37-39, 41, 43, and 44 under 35 U.S.C. § 103(a) as allegedly being un-patentable over Piran et al. (US Pat. No. 5,705,338) in view of Hendrickson et al. (Nucleic Acid Research 23(3):522-529, 1995). The Examiner alleges that Piran et al. teach a method for detecting a compound of interest in a sample similar to the element of the claimed invention, except for using a nucleic acid label or detection of the nucleic acid label. The Examiner further alleges that the Hendrickson et al.'s teaching makes up for the

shortcomings of Piran et al. The Examiner, therefore, alleges that the claimed invention would have been obvious to one of ordinary skill in view of the cited references.

Applicant respectfully disagrees with the Examiner's characterization that the teachings of Piran et al. and Hendrickson et al. make the claimed invention obvious. Neither Piran et al. or Hendrickson et al., separately or together, teach, suggest, motivate, or make obvious each and every elements of the claimed invention.

The Applicant respectfully disagrees with the Examiner for a number of reasons. In their abstract, Piran et al. describe an assay method that uses: 1) an insoluble material attached to an analyte derivative (to capture unbound antibody); and 2: a solid phase carrying a binder (for solid phase capture and removal of antibody-bound analyte. The requirement for solid phase capture and separation of analyte-bound and labeled antibody is a key difference between Piran et al.'s technique and the claimed invention. The Abstract of the Piran et al. reference clearly states "The solid phase is then separated, and the label attached to the solid phase is measured." The goal and purpose of the claimed invention, which has not been made obvious by Piran et al. and/or Hendrickson et al., either together or separately, is to detect the analyte of interest in the solution phase, that is, detection is done without the presence of any solid support in connection with the construct-compound complexes that are being detected, which is very different and non-obvious from detecting the analyte of interest that has attached to or has been captured by a solid support. The techniques of the claimed invention remove only unbound binding construct (labeled antibody fragment). Secondly, the claimed invention does not have to use an "analyte mimic", but instead, uses a binding domain that is specific to the antibody variable region or an "epitope mimetic." The preferred mimetic for the claimed invention is a peptide that does not have to look anything at all like the analyte of interest. The only requirement is that the mimetic bind specifically to the variable region of the antibody fragment or recombinant antibody binding domain. Furthermore, the amino acid sequence of the mimetic can be altered by a single amino acid to induce subtle changes in affinity for the variable region in efforts to optimize removal of unbound binding constructs. Finally, and importantly, the claimed invention requires a single binding domain for use in a binding construct as apposed to one or more binding domains as, for example, in an intact antibody molecule. The requirement for a single binding domain is crucial

for sensitivity. In the techniques of Piran et al., and further in view of Hendrickson et al., anything less than an almost complete saturation of the labeled antibody binding sites by analyte of interest will result in bridging (by virtue of two antibody binding domains) of bound analyte to insoluble-analyte mimetic, preventing antibody binding to the solid support and dramatically reducing sensitivity. None of the described advantages of the claimed invention is made obvious by the Piran et al. assay and/or Hendrickson et al.

In Figures 1-4 of the Piran et al. patent, there is an absolute requirement for solid phase removal and detection of analyte of interest associated with the solid phase. In addition, the first claim of their patent clearly distinguishes it from the claimed invention. Claim 1 of the Piran et al. patent requires several steps that involve mixing sample with analyte, then adding insoluble material to form "... an insoluble material-labeled specific binder complex." Then adding a second binder "... which binds to one portion of the analyte -labeled specific binder complex, such second binder being attached to a solid phase, such that the insoluble material, by binding to the labeled-specific binder, that had not bound analyte, inhibits the binding of the unreacted labeled specific binder to the solid phase." Unless the labeled specific binder is monovalent this last step only occurs effectively at very high analyte concentration. An alternative may be that only bivalent antibody will bind to the insoluble material-analyte derivative or mimic or that binding will sterically inhibit the solid phase second binder from binding. No matter the reason, these requirements and steps and a final wash (Claim 1c) teach away from the claimed invention.

The present invention was specifically designed for exquisite sensitivity afforded by a single binding domain in the construction of the binding construct and for detection of analyte of interest in the solution phase and not that captured or sandwiched on a solid support. The claimed invention requires a single binding domain, a mimetic to the antibody variable region, not an analyte derivative or mimic, no solid phase capture of analyte and no wash step. The use of a bivalent antibody molecule by Piran and Hendrickson and the requirement for solid phase capture of analyte of interest are among the main causes of many of the background issues and/or inadequate sensitivity associated with these technologies. They become multi-step, complicated, procedural assays that explain, in part, the reasons why they are still not in common usage today.

The present invention was specifically designed to overcome some of these problems, is unique, and the solution it offers is not anticipated or made obvious by the cited references.

Because of the fundamental differences between the disclosure of Piran et al. and Hendrickson et al. compared to the claimed invention, the Applicant respectfully disagrees with the Examiner's allegation on page 5 of the Official Communication of June 5th, 2006, which states:

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the nucleic acid label to the labeled antibodies of Piran, et al. ... and have been motivated ... for the expected benefit of obtaining 'ultra-sensitive' multi-analyte detection as taught by Hendrickson, et al...

It is respectfully asserted that the Examiner is incorrect in this allegation. The fact is the bridging effect with analyte mimetic of less than saturated, bivalent antibody binding to analyte and the reduced sensitivity associated with this type of binding was not obvious and would certainly not lead to "ultra-sensitive" detection using Piran et al. in view of Hendrickson et al. Bridging is the ability of bivalent antibody to simultaneously bind to soluble antigen and antigen bound to a solid support. The present invention was specifically designed to overcome the "bridging" problem and to avoid solid phase capture and wash steps. Claimed invention is unique and not made obvious by the combination of these two publications.

Based on the foregoing, Piran et al. and Hendrickson et al., either separately or together, do not teach, suggest, or provide motivation to make the claimed invention obvious. Thus, the claimed invention is not obvious under 35 U.S.C. § 103(a). Accordingly, Applicant respectfully requests that this rejection be withdrawn.

**APPLICANT'S CLAIMED INVENTION IS NOT OBVIOUS UNDER 35 U.S.C. § 103(A) IN VIEW OF THE REFERENCES CITED BY THE EXAMINER**

The Examiner rejected claims 20, 21, 42, and 43 under 35 U.S.C. § 103(a) as allegedly being un-patentable over Piran et al. (US Pat. No. 5,705,338) in view of Hendrickson et al. (Nucleic Acid Research 23(3):522-529, 1995), and further in view of Baez et al (6,511,809). The Examiner alleges that Piran et al. teach a method for detecting a compound of interest in a sample

similar to the element of the claimed invention, except for using a nucleic acid label or detection of the nucleic acid label. The Examiner further alleges that the Hendrickson et al.'s teaching makes up for the shortcomings of Piran et al except for the teaching of RNA, which the Examiner alleges is taught by Baez et al. The Examiner, therefore, alleges that the claimed invention would have been obvious to one of ordinary skill in view of the cited references.

Applicant discussed the shortcomings Piran et al. and Hendrickson et al. above, and Applicant discussed the shortcomings of Baez et al. in a response to a previous Office Action for this case, which Applicant incorporates herein by reference. Piran et al., Hendrickson et al, and/or Baez et al., either separately or together do not teach each and every step of the claimed invention, in particular the claimed invention requires that detection of analyte of interest be done in solution phase. The cited references do not report such solution phase detection. The goal and purpose of the claimed invention, which has not been made obvious by the cited references, either together or separately, is to detect the analyte of interest in the solution phase, that is, detection is done without the presence of any solid support in connection with the construct-compound complexes that are being detected, which is very different and non-obvious from detecting the analyte of interest that has attached to or has been captured by a solid support. In contrast to cited references the claimed invention requires no solid phase capture of analyte and no wash step.

Based on the foregoing, Piran et al., Hendrickson et al., and/or Baez et al., either separately or together, do not teach, suggest, or provide motivation to make the claimed invention obvious. Thus, the claimed invention is not obvious under 35 U.S.C. § 103(a). Accordingly, Applicant respectfully requests that this rejection be withdrawn.

#### **APPLICANT'S CLAIMED INVENTION IS NOT OBVIOUS UNDER 35 U.S.C. § 103(A) IN VIEW OF THE REFERENCES CITED BY THE EXAMINER**

The Examiner rejected claims 4, 5, 26, and 27 under 35 U.S.C. § 103(a) as allegedly being un-patentable over Ullman et al. (US Pat. No. 6,797,481) in view of Piran et al. (US Pat. No. 5,705,338). The Examiner alleges that Ullman et al. teach a method for detecting a compound of interest in a sample similar to the element of the claimed invention, except for using magnetic

particles or magnetic means for particle separation. The Examiner further alleges that the Piran et al.'s teaching makes up for the shortcomings of Ullman et al. The Examiner, therefore, alleges that the claimed invention would have been obvious to one of ordinary skill in view of the cited references.

Applicant discussed the shortcomings Ullman et al. and Piran et al. above. Ullman et al. and/or Piran et al., either separately or together do not teach each and every step of the claimed invention, in particular the claimed invention requires that detection of analyte of interest be done in solution phase. The cited references do not report such solution phase detection. The goal and purpose of the claimed invention, which has not been made obvious by the cited references, either together or separately, is to detect the analyte of interest in the solution phase, that is, detection is done without the presence of any solid support in connection with the construct-compound complexes that are being detected, which is very different and non-obvious from detecting the analyte of interest that has attached to or has been captured by a solid support. Again, in contrast to cited references the claimed invention requires no solid phase capture of analyte and no wash step.

Based on the foregoing, Ullman et al. and/or Piran et al., either separately or together, do not teach, suggest, or provide motivation to make the claimed invention obvious. Thus, the claimed invention is not obvious under 35 U.S.C. § 103(a). Accordingly, Applicant respectfully requests that this rejection be withdrawn.

#### **APPLICANT'S CLAIMED INVENTION IS NOT OBVIOUS UNDER 35 U.S.C. § 103(A) IN VIEW OF THE REFERENCES CITED BY THE EXAMINER**

The Examiner rejected claims 4, 5, 26, and 27 under 35 U.S.C. § 103(a) as allegedly being un-patentable over Ullman et al. (US Pat. No. 6,797,481) in view of Baez et al. (6,511,809). The Examiner alleges that Ullman et al. teach a method for detecting a compound of interest in a sample similar to the element of the claimed invention, except for using DNA or RNA label. The Examiner further alleges that the Baez et al.'s teaching makes up for the shortcomings of Ullman



et al. The Examiner, therefore, alleges that the claimed invention would have been obvious to one of ordinary skill in view of the cited references.

Applicant discussed the shortcomings Ullman et al. and Baez et al. above. Ullman et al. and/or Baez et al., either separately or together do not teach each and every step of the claimed invention, in particular the claimed invention requires that detection of analyte of interest be done in solution phase. The cited references do not report such surfaces solution phase detection. The goal and purpose of the claimed invention, which has not been made obvious by the cited references, either together or separately, is to detect the analyte of interest in the solution phase, that is, detection is done without the presence of any solid support in connection with the construct-compound complexes that are being detected, which is very different and non-obvious from detecting the analyte of interest that has attached to or has been captured by a solid support. Again, in contrast to cited references the claimed invention requires no solid phase capture of analyte and no wash step.

Based on the foregoing, Ullman et al. and/or Baez et al., either separately or together, do not teach, suggest, or provide motivation to make the claimed invention obvious. Thus, the claimed invention is not obvious under 35 U.S.C. § 103(a). Accordingly, Applicant respectfully requests that this rejection be withdrawn.

#### **APPLICANT'S CLAIMED INVENTION IS NOT OBVIOUS UNDER 35 U.S.C. § 103(A) IN VIEW OF THE REFERENCES CITED BY THE EXAMINER**

The Examiner rejected claims 11, 21, 33, and 43 under 35 U.S.C. § 103(a) as allegedly being un-patentable over Ullman et al. (US Pat. No. 6,797,481) in view of Hendrickson et al. (6,511,809). The Examiner alleges that Ullman et al. teach a method for detecting a compound of interest in a sample similar to the element of the claimed invention, except for amplification of the label by PCR. The Examiner further alleges that the Hendrickson et al.'s teaching makes up for the shortcomings of Ullman et al. The Examiner, therefore, alleges that the claimed invention would have been obvious to one of ordinary skill in view of the cited references.

Applicant discussed the shortcomings Ullman et al. and Hendrickson et al. above. Ullman et al. and/or Hendrickson et al., either separately or together do not teach each and every step of the claimed invention, in particular the claimed invention requires that detection of analyte of interest be done in solution phase. The cited references do not report such surfaces solution phase detection. The goal and purpose of the claimed invention, which has not been made obvious by the cited references, either together or separately, is to detect the analyte of interest in the solution phase, that is, detection is done without the presence of any solid support in connection with the construct-compound complexes that are being detected, which is very different and non-obvious from detecting the analyte of interest that has attached to or has been captured by a solid support. Again, in contrast to cited references the claimed invention requires no solid phase capture of analyte and no wash step.

Based on the foregoing, Ullman et al. and/or Hendrickson et al., either separately or together, do not teach, suggest, or provide motivation to make the claimed invention obvious. Thus, the claimed invention is not obvious under 35 U.S.C. § 103(a). Accordingly, Applicant respectfully requests that this rejection be withdrawn.

#### **PRIOR ART MADE OF RECORD AND NOT RELIED UPON**

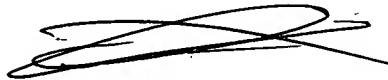
Finally, the Examiner cites Boguslaski et al. (US Pat. No. 4,134,792) as pertinent to Applicant's disclosure.

The applicant respectfully disagrees with this assessment. The Boguslaski et al. patent is for a method to detect a compound in solution that uses an enzyme modulator as a labeling substance that is coupled to a binding component of the binding reaction system (modulator conjugate - Column 2, line 40). Several assay formats are described. The amount of unbound modulator conjugate remaining in solution is an indication of the amount of analyte of interest in the sample. This is an important distinction when comparing this technology to the present invention. The claimed invention measures the amount of bound, binding construct left in solution not the effect of the unbound binding construct left behind.

Applicant respectfully submits that the claims are ready for examination and in condition for allowance.

Respectfully submitted,

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